PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference PCA30854/HMY	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. **PCT/KR2003/002171**	International filing date *(day/month/year)* **17 OCTOBER 2003 (17.10.2003)**	Priority date *(day/month/year)* 18 OCTOBER 2002 (18.10.2002)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07D 413/14

Applicant

HANMI PHARM. CO., LTD. et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
06 FEBRUARY 2004 (06.02.2004)	04 FEBRUARY 2005 (04.02.2005)

Name and mailing address of the IPEA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
LEE, Jae Jeong
Telephone No. 82-42-481-5604

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International aplication No.
PCT/KR2003/002171

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[ ] the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

[ ] the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statment) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

[ ] the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

[ ] the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application(under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/ or 55.3).

3. With regard to any **nucleotide** and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained inthe international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disc losure in the international applicationas as filed has been furinshed.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages _____

[ ] the claims, Nos. _____

[ ] the drawings, sheets _____

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box(Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed." and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION

International aplication No.
PCT/KR2003/002171

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1 - 6	YES
	Claims		NO
Inventive step (IS)	Claims	1 - 6	YES
	Claims		NO
Industrial applicability (IA)	Claims	1 - 6	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: ES 2050069 A1 (Vita-Invest, S.A.) 01 May 1994
D2: EP 0196132 A2 (Janssen Pharmaceutica N.V.) 01 Oct. 1986
D3: WO 0212200 A1 (Teva Pharmaceuticals) 14 Feb. 2002
D4: WO 0185731 A1 (RPG Life Sciences Ltd.) 05 May 2000

The claims 1 - 6 of the present invention relate to an improved method for preparing risperidone (3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one) by reacting 2,4-difluorophenyl(4-piperidinyl)methanone oxime hydrochloride and 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one in an aqueous alkali hydroxide solution in the range of 20 to 40%.

D1 discloses a preparation method of risperidone in 3 steps: (1) condensation of pyridopyrimidine derivatives with (difluorobenzoyl)piperidine; (2) oximation of the resultant compound with NH2OH.HCl; (3) cyclization of the oxime under basic condition.
D2 concerns novel 1,2-benzisoxazol-3-yl and 1,2-benzisothiazol-3-yl derivatives, methods of preparing said compounds and pharmaceutical compositions having antipsychotic properties.
D3 is directed to the novel polymorphic forms of risperidone, and processes for making risperidone. Pharmaceutical compositions containing the new forms of risperidone and methods of using them are also disclosed.
D4 describes a process for the preparation of risperidone comprising condensation of 3-substituted ethyl-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one with 6 fluoro-3-(4-piperidinyl)-1,2-benzosoxazole in water in the presence of an inorganic base.

Although D1-D4 teach the process for preparing and using various types of risperidone, D1-D4 do not disclose the features of the subject matter of claims 1 - 6, which meet the criteria set forth in PCT Article 33(2), (3) and (4). The improved method for preparing risperidone by reacting 2,4-difluorophenyl(4-piperidinyl)methanone oxime hydrochloride and 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one in an aqueous alkali hydroxide solution in the range of 20 to 40% is not anticipated by any of the references on record.

Thus, the invention described in the present application is considered to be novel, inventive and industrially applicable.